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*Original Research*

# High doses of methylprednisolone in patients with severe COVID-19 infection



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**Abstract**

Aim: Hypoxemia caused by lung injury is a typical feature of SARS- CoV-2 Pneumonia. Although corticosteroids are not the definite treatment for this condition, they have proven to be effective in some cases. In this study, we aimed to determine if high doses of methylprednisolone are safe and effective in patients suffering from severe SARS-COV-2 pneumonia.

Material and Methods: In all, 78 patients were enrolled in the study. The randomized double-blinded study involved half of the patients receiving methylprednisolone and half receiving a placebo. The primary outcome, calculated by comparing the percentage of in-hospital deaths between the two groups, was not statistically significant. In the Methylprednisolone group, patients had decreased lung compliance, increased oxygen demand, and an increased risk of infections, as measured by procalcitonin levels.

Results: A total of 78 patients were divided equally to get a placebo or pulse methylprednisolone in this double-blinded, randomized control trial. The study included 64.1% (50) female participants and 35.9% (28) male participants. Serum Ferritin levels were significantly increased in the placebo group in comparison to the methylprednisolone group. Procalcitonin was increased in the methylprednisolone group. The requirement for oxygen inhalation was lower in the placebo group. The total hospital stays, and days spent on mechanical ventilation were longer in patients who survived.

Discussion: Methylprednisolone use in severe COVID-19 infections did not improve survival compared to placebo. Furthermore, methylprednisolone significantly increased the risk of infection.

**Keywords**

SARS-COV-2 Infection, Methylprednisolone, Mechanical Ventilation

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## Introduction

A worldwide pandemic caused by SARS Corona Virus 2 (SARS-CoV-2) gripped the world in 2019, infecting more than 590 million people and claiming 6.4 million lives. The majority of patients recover well, but 14% develop severe pneumonia and 5% develop critical pneumonia [1]. Lung damage, acute respiratory distress syndrome, and respiratory failure are the most common causes of death in patients. Lymphopenia with low CD4 and CD8 lymphocytes may be associated with disease activity and poor prognosis [2]. Key histological features include exudative diffuse alveolar damage, capillary congestion, and microthrombi [3,4].

Infection can be controlled by a well-adjusted immune response, but lung injury can result from an extravagant response. A cytokine storm is induced by impaired gaseous exchange and alveolar patency caused by neutrophils and macrophages, resulting in lung injury and the release of IL-1, IL-6, and TNF alpha by infected cellular debris [5]. Due to their ability to suppress immune functions by impairing the innate immune system, corticosteroids have been widely discouraged because of the fear of worsening viral transmission. However, the development of severe or critical pneumonia in patients receiving long-term maintenance doses of steroids is not associated with COVID-19 [6]. The Multinational Surviving Sepsis Guideline in COVID-19 recommends giving steroids to patients with severe COVID-19 who have ARDS on mechanical ventilation (based on very limited evidence) [7]. However, a study conducted on COVID-19 patients with the RECOVERY Trial has shown that using dexamethasone, a corticosteroid, as a treatment for severe COVID-19 requiring oxygen therapy or a mechanical ventilator improved the outcome significantly [8]. Similar to influenza, Middle East respiratory syndrome, or severe acute respiratory syndrome, steroids have a well-established role in viral pneumonias [9]. Glucocorticoids are used in pulse doses in order to combat cytokine storms leading to ARDS, disseminated intravascular coagulation, shock and death, and to reduce affliction and mortality [10]. This study aimed to evaluate the effectiveness of high-dose methylprednisolone in patients with severe SARS-CoV-2 pneumonia.

## Material and Methods

The study was conducted at the Intensive Care Unit, Pakistan Institute of Medical Sciences, Islamabad, between January 2021 and December 2021, as a single-center, double-blind, randomized, controlled parallel group study. This trial was registered with the Iranian Registry of Clinical Trials (IRCT) under the number IRCT20200723048178N3. Ethical approval was granted by the Ethical Review Board (ERB) of Shaheed Zulfiqar Ali Bhutto Medical University on 28 April 2021, No. F.1-1/2015/ERB/SZABMU/771. Patients were enrolled only after informed consent. All data of the patients were kept confidential except for the researchers and the patient.

A total of 78 patients were randomized using a "simple" randomization method that considered individuals as one unit. With the help of "https://www.randomizer.org/", a random number table was generated. Two groups of patients were labelled "controls" and "interventional". The caregivers (ICU nurse) and patients were blinded.

### *Setting*

This study included patients (>18 years) who were confirmed positive for SARS-CoV-2 by Real-Time Polymerase Chain Reaction (RT-PCR). The study included patients with severe COVID-19 infections. COVID-19 infection is defined as patients whose oxygen saturation is 94% on room air, whose arterial partial pressure of oxygen to fraction of inspired air ratio is 300mm Hg, whose respiratory rate exceeds 30 breaths per minute, or whose radiological images indicate a lung infiltrate of > 50% [11]. According to standard guidelines, all patients received dexamethasone 6 mg for a minimum of three days [8]. Patients with HIV infection, active tuberculosis, pulmonary tuberculosis history, creatinine clearance (CrCl) of less than 30 ml/minute, an ejection fraction of 30% or less, advanced liver disease, and methylprednisolone allergy were excluded from the study.

### *Data collection*

Two groups of 39 people each were formed. On one arm, 1000 mg of Methylprednisolone (Solumedrol®) was infused into 100 ml of normal saline once daily for three days, diluted in 100 ml of water. The other arm received 100 ml of normal saline (placebo). Infusion bottles were numbered so that the nurse administering the fluid was unaware of which bottles contained the actual medication. Oxygen therapy, ventilator support, antiviral drugs (remdesivir), antibiotics, fluids, PPIs, and anticoagulants were all administered to the patients.

### *Outcomes*

The primary outcome was the in-hospital mortality between the two groups after 28 days. The total duration of hospital stay, change in the inflammatory markers (i-e. C-Reactive Protein (CRP), InterLeukin-6 (IL-6)) before and after treatment with methylprednisolone, days on Mechanical Ventilation (MV), changes in the requirement of oxygen as measured by the Fraction of inspired Oxygen (FiO2), Positive End-Expiratory Pressure (PEEP), and static lung compliance (C-Diff) were the secondary outcomes.

### *Data Analysis procedure*

Data were analyzed using SPSS version 25. The primary outcome was mortality at 28 days after enrollment. The comparisons were conducted according to the intention-to-treat principle. A total of 78 patients were included in the study.

Secondary outcomes i-e the total duration of hospital stay, change in the inflammatory markers before and after treatment with methylprednisolone, days on Mechanical Ventilation (MV), changes in the requirement of oxygen as measured by the Fraction of inspired Oxygen (FiO2), Positive End-Expiratory Pressure (PEEP), and static lung compliance (C-Diff) were measures as mean differences between the methylprednisolone and the placebo group. The same comparison was done in the discharged and death groups. This study was performed at Pakistan Institute of Medical Sciences, and all investigators were unaware of patients' treatment assignments.

### *Ethical Approval*

Ethics Committee approval for the study was obtained.

## Results

In total, 78 patients participated in the study. Supportive care and conventional treatment were provided to all patients.

**Table 1.** Baseline characteristics before and after treatment between groups of the study participants.

| Variables | Groups | N | Before treatment (mean) | SD | P-value | N | After Treatment (mean) | SD | P-value |
|---|---|---|---|---|---|---|---|---|---|
| CRP | Methylprednisolone | 39 | 129.90 | 68.19 | 0.11 | 39 | 81.56 | 62.38 | 0.03 |
| | Placebo | 39 | 230.95 | 379.07 | 0.11 | 39 | 188.56 | 293.77 | 0.03 |
| Ferritin | Methylprednisolone | 39 | 1634.80 | 1446.55 | 0.22 | 39 | 807.99 | 912.40 | 0.002 |
| | Placebo | 39 | 1322.14 | 623.53 | 0.22 | 39 | 1459.99 | 836.14 | 0.002 |
| IL-6 | Methylprednisolone | 39 | 379.69 | 736.10 | 0.05 | 39 | 615.55 | 974.63 | 0.003 |
| | Placebo | 37 | 138.23 | 168.73 | 0.05 | 37 | 115.44 | 104.38 | 0.003 |
| D-Dimers | Methylprednisolone | 39 | 2905.96 | 1997.37 | <0.01 | 39 | 3239.13 | 2261.34 | <0.01 |
| | Placebo | 39 | 1068.81 | 994.16 | <0.01 | 39 | 1223.13 | 1619.10 | <0.01 |
| Procalcitonin | Methylprednisolone | 36 | 0.233 | 0.27 | 0.002 | 36 | 1.25 | 2.2 | <0.01 |
| | Placebo | 36 | 0.999 | 1.34 | 0.002 | 36 | 0.28 | 0.35 | <0.01 |
| Days on MV | Methylprednisolone | 39 | 17.31 | 5.247 | <0.01 | 27 | 13.67 | 5.55 | <0.01 |
| | Placebo | 39 | 7.31 | 4.730 | <0.01 | 39 | 9.26 | 3.97 | <0.01 |
| Total Hospital stay | Methylprednisolone | 39 | 19.54 | 5.41 | <0.01 | 39 | | | |
| | Placebo | 39 | 9.62 | 6.4 | <0.01 | 39 | | | |
| $FiO_2$ | Methylprednisolone | 39 | 90.51 | 15.89 | 0.01 | 39 | 63.85 | 19.00 | 0.42 |
| | Placebo | 39 | 97.95 | 7.32 | 0.01 | 39 | 59.74 | 25.5 | 0.42 |
| PEEP | Methylprednisolone | 39 | 10.79 | 2.39 | <0.01 | 39 | 9.38 | 2.86 | <0.01 |
| | Placebo | 39 | 8.10 | 1.71 | <0.01 | 39 | 6.54 | 2.47 | <0.01 |
| C-STAT | Methylprednisolone | 34 | 21.46 | 3.19 | 0.40 | 34 | 26.21 | 4.21 | 0.10 |
| | Placebo | 39 | 20.9 | 9.62 | 0.431 | 39 | 22.85 | 11.71 | 0.12 |

(Abbreviations: N= number of patients, SD = Standard Deviation, CRP = C-Reactive Protein, IL-6 = InterLeukin-6, MV = Mechanical Ventilation, FiO2 = Fraction of inspired Oxygen, PEEP = Positive End-Expiratory Pressure, C-Stat = Static Lung Compliance)

**Table 2.** Difference in variables after intervention.

| Difference (Before and After Treatment | Groups | N | Mean | SD | p-value |
|---|---|---|---|---|---|
| CRP | Methylprednisolone | 39 | 48.3 | 79.61 | 0.80 |
| | Placebo | 39 | 42.38 | 120.06 | |
| Ferritin | Methylprednisolone | 39 | 8.27 | 934.97 | <0.01 |
| | Placebo | 39 | -1.38 | 380.92 | |
| IL-6 | Methylprednisolone | 39 | -235.85 | 1031.21 | 0.127 |
| | Placebo | 37 | 22.79 | 106.77 | |
| D- Dimers | Methylprednisolone | 39 | -333.17 | 1861.58 | 0.667 |
| | Placebo | 39 | -154.32 | 1791.88 | |
| Procalcitonin | Methylprednisolone | 36 | -0.97 | 2.9 | <0.01 |
| | Placebo | 36 | 0.73 | 1.35 | |
| $FiO_2$ | Methylprednisolone | 39 | 26.67 | 15.95 | 0.032 |
| | Placebo | 39 | 38.21 | 28.62 | |
| PEEP | Methylprednisolone | 39 | 1.41 | 2.82 | 0.805 |
| | Placebo | 39 | 1.56 | 2.65 | |
| C-STAT | Methylprednisolone | 39 | -4.74 | 3.97 | 0.024 |
| | Placebo | 34 | -2.76 | 3.24 | |

(Abbreviations: N= number of patients, SD = Standard Deviation, CRP = C-Reactive Protein, IL-6 = InterLeukin-6, MV = Mechanical Ventilation, FiO2 = Fraction of inspired Oxygen, PEEP = Positive End-Expiratory Pressure, C-Stat = Static Lung Compliance)

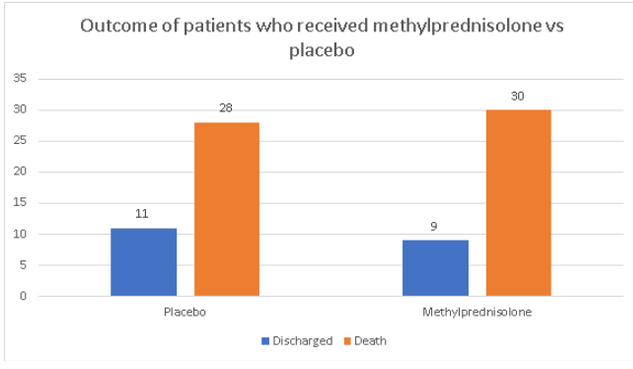


**Figure 1.** Comparison of mortality in patients who received methylprednisolone vs placebo (P value 0.796).

Pulsed methylprednisolone was administered to half of the patients, while placebos were administered to the other half.

The study included 64.1% (50) female participants and 35.9% (28) male participants. Table 1 summarizes the baseline characteristics of study participants before and after treatment between groups.

Table 2 shows the difference in variables after the intervention. The difference was calculated by subtracting the value of a variable after the intervention from the baseline value.

There was a significant increase in ferritin levels in patients who received a placebo compared to those who received methylprednisolone (P value 0.001). Compared to the placebo group, methylprednisolone significantly increased procalcitonin

**Table 3.** Comparison of mortality outcomes after the intervention.

| Difference (Before and After Treatment | Outcome | N | Mean | SD | p- value |
|---|---|---|---|---|---|
| CRP | Dead | 58 | 33.84 | 110.91 | 0.087 |
| | Discharge | 20 | 78.75 | 55.29 | |
| Ferritin | Dead | 58 | 238.53 | 774.55 | 0.063 |
| | Discharge | 20 | 651.75 | 1029.62 | |
| IL-6 | Dead | 56 | -16.53 | 670.76 | 0.120 |
| | Discharge | 20 | -371.48 | 902.85 | |
| D- Dimers | Dead | 58 | -256.10 | 2047.56 | 0.919 |
| | Discharge | 20 | -207.90 | 897.84 | |
| Procalcitonin | Dead | 52 | -.215 | 1.80 | 0.502 |
| | Discharge | 20 | .13 | 2.31 | |
| $FiO_2$ | Dead | 58 | 25.17 | 21.86 | <0.01 |
| | Discharge | 20 | 53.50 | 14.88 | |
| PEEP | Dead | 58 | .74 | 2.54 | <0.01 |
| | Discharge | 20 | Mar.65 | 1.98 | |
| C-STAT | Dead | 53 | -3.09 | 4.00 | <0.01 |
| | Discharge | 20 | -5.75 | 2.7 | |

(Abbreviations: N= number of patients, SD = Standard Deviation, CRP = C-Reactive Protein, IL-6 = InterLeukin-6, MV = Mechanical Ventilation, FiO2 = Fraction of inspired Oxygen, PEEP = Positive End-Expiratory Pressure, C-Stat = Static Lung Compliance)

levels (p-value (<0.001). FiO2 showed significant reductions in oxygen requirements in patients receiving placebo compared to methylprednisolone (p-value 0.032). Static Lung Compliance (C-stat) increased in the methylprednisolone group (p-value 0.024), but there was no effect on PEEP values in either group. Patients with high oxygenation requirements died more frequently. This was seen as the number of deaths was more in patients whose mean change in the FiO2 values was less compared to those whose FiO2 dropped significantly. A significant reduction in peep requirements from baseline was also associated with mortality benefits (p-value 0.001). The C-Stat values, on the other hand, were positively associated with improved outcomes (p-value 0.001).

The total hospital stay and the number of days spent on mechanical ventilation were longer in patients who survived. Patients who died spent an average of 11.45±7.27 days on mechanical ventilation compared to 14.8±5.93 days in those who survived (p=0.067). Additionally, the mean length of hospital stays in patients who died was 14.16±9.45 compared to 19.15±5.8 in patients who survived (p-value 0.008).

## Discussion

We found no improvement in the hospital mortality in patients receiving standard care and 1000mg of methylprednisolone for 3 days than in patients receiving standard care and placebo, rather a worsening of mortality. In terms of secondary outcome, Ferritin levels significantly increased in placebo-treated patients compared to methylprednisolone-treated patients. D-dimers and IL-6 worsened after therapy, but CRP improved but was not statistically significant. Methylprednisolone therapy significantly increased procalcitonin levels. FiO2 significantly decreased in patients receiving a placebo versus methylprednisolone (p-value 0.032). PEEP values did not change in either group and high-dose pulse therapy did not shorten hospital stays.

Although steroids have been extensively used in syndromes closely linked to COVID-19 like SARS, Middle East Respiratory Syndrome, MERS, influenza, and community-acquired pneumonia, the evidence to support or reject the use of glucocorticoids in such circumstances is weak due to the lack of RCTs [12- 15]. In viral infections, glucocorticoids are associated with favorable outcomes based on patient selection, dosage, type, and time from infection. In patients treated with systemic glucocorticoids for MERS, SARS, or influenza, viral clearance is slow [13,16,17].

The strengths of corticosteroids used in available publications are not homogeneous [18]. The two main evidentiary drugs used extensively are dexamethasone and remdesivir [19]. In a study conducted at Bellvitge University Hospital, a tertiary care hospital with 750 beds in Barcelona (Spain), similar outcomes were observed. Two groups of patients were treated with methylprednisolone 100 mg/day pulses for three days (189 patients) and dexamethasone 6 mg/day for 10 days (493 patients). In-patient hospital mortality, invasive ventilation, critical care admissions, and time spent in hospitals before discharge were significantly higher in the methylprednisolone group as depicted in our study.

Despite the improvements in CRP, the results of both the dexamethasone and methylprednisolone groups were comparable in terms of inflammatory markers. However, our study found a slight improvement in CRP, but not statistically significant, but worsening of other inflammatory markers after receiving pulse steroids. This study differed from the Spain study in that we administered pulse steroids to ICU patients who were on mechanical ventilation, whereas the Spanish study involved patients who were not on mechanical ventilation [20].

According to a Brazilian double-blind placebo-controlled trial, methylprednisolone was not advantageous in treating COVID-19 pneumonia patients with SpO2 greater than 94% at room air or in need of noninvasive or invasive ventilation. Among those given methylprednisolone 0.5 mg/kg/12h or placebo for five days, 28-day mortality rates were 37.1% and 38.2%, respectively [21].

In our study, the proportion of patients developing septic shock was higher in the pulse steroid group than in the placebo group as reflected by high procalcitonin levels in the corticosteroid-receiving group. The use of steroids in viral syndromes and influenza increases the risk of secondary bacterial and fungal infections [22].

Dexamethasone has been widely used in hospitalized patients worldwide as a result of the results of the RECOVERY trial [8]. There is a better mortality outcome for COVID positive patients who receive dexamethasone during the first week of their disease and require oxygen support. This indicates that immunopathological factors could play a role at a given stage of a disease, accompanied by active virus replication.

Since this study was conducted in a tertiary care hospital in an area requiring a high number of referred patients with severe diseases, one reason for the high mortality rate may have been the fact that patients included in our study had severe diseases and all required mechanical ventilation. The observed outcomes might have been affected by a different time and period of corticosteroid administration.

## *Conclusion*

In this study, we found that high-dose methylprednisolone did not improve survival in patients with SARS-CoV-2 infected patients as compared to the placebo. Significant decreases in some of the inflammatory markers were seen in the methylprednisolone group as compared to placebo. Large multicentred studies with high power are required to confirm the findings in our study.

***Scientific Responsibility Statement***

*The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.*

***Animal and human rights statement***

*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.*

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***Conflict of interest***

*The authors declare no conflict of interest.*

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